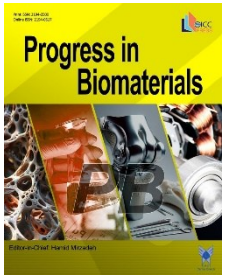


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# Osseointegration and Host Immune Response to Zirconia Implants: Current Evidence and Perspectives

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**Review Article**

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**Abstract**

**Background:** Zirconia dental implants are increasingly explored as alternatives to titanium due to favorable osteointegration and biocompatibility.

**Objective:** To review the osseointegration potential, immune response, and clinical relevance of zirconia implants, with attention to strategies aimed at improving performance.

**Results:** Osseointegration is influenced by surface roughness, chemistry, and implant design. Surface treatments such as sandblasting, acid etching, laser structuring, and bioactive coatings improve topography, wettability, and osteoblast activity. Zirconia demonstrates high biocompatibility and generally favorable immune responses, including reduced inflammatory signaling and support for tissue healing, although clinical data remain limited. Its smooth surface and low plaque affinity may further support peri-implant tissue health. Emerging innovations in mechanical reinforcement, antibacterial modifications, and digital workflows, offer additional potential to enhance implant performance.

**Conclusion:** Zirconia implants exhibit promising osseointegration and biocompatibility, but current evidence is insufficient to claim superiority over titanium. Further long-term clinical studies are required to validate these findings and optimize implant design and surface strategies.

**Keywords:** Dental implant; Zirconia implant; Osseointegration; Immune Response; Biocompatibility

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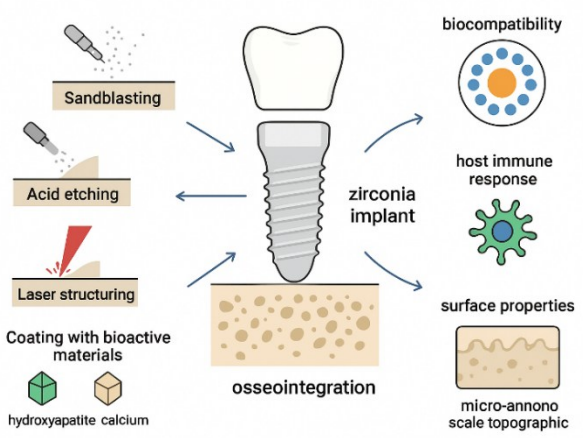

## 1. Introduction

Dental implantology has become a cornerstone of restorative dentistry, providing reliable long term solutions for replacing missing teeth and restoring function, aesthetics, and quality of life [1] [2]. Since Brånemark's discovery of osseointegration in the 1960s, implants, primarily titanium, have achieved high survival rates and transformed oral rehabilitation [3] [4]. Titanium's strength, corrosion resistance, and biocompatibility make it the traditional choice; however, concerns such as hypersensitivity, ion release, peri-implantitis, and esthetic drawbacks have driven the search for alternatives [5] [6]. Zirconia ($ZrO_2$) has gained attention for its high strength, fracture toughness, wear resistance, and superior esthetics due to its tooth-like color [7-10]. As plaque (a biofilm of bacteria) is the main trigger for peri-implant inflammation, zirconia's low plaque affinity further supports use in patients with inflammatory or allergic conditions [11]. With advances in surface modification and growing clinical evidence, zirconia implants are increasingly considered not just an alternative, but in some cases a preferred option [12].

While zirconia has increasingly demonstrated its utility as a dental implant material, its biological performance particularly in terms of osseointegration remains a subject of ongoing scientific investigation and clinical scrutiny. Osseointegration, the cornerstone of dental implant success, refers to the formation of a direct, functional, and stable interface between the implant surface and the surrounding living bone. This biological process is essential for providing long term mechanical stability and load bearing capacity, enabling the implant to withstand masticatory forces and function as a natural tooth root substitute. It is influenced by multiple factors, including the implant material, surface properties, host bone quality, systemic health conditions, and local immune responses [13,14]. In this context, zirconia implants have shown encouraging results. Numerous in vivo studies and clinical trials have demonstrated that zirconia can form a stable bone to implant interface, with histological evidence of new bone formation [15,16]. Surface treatments such as sandblasting [17], acid etching [18], laser modification [19], and coatings with bioactive materials like hydroxyapatite [20] have further enhanced the potential of zirconia to support osseointegration by improving surface roughness, wettability, and bioactivity. However, despite these advancements, the efficiency of zirconia is often compared to titanium, the benchmark material with decades of proven success [18].

Beyond the mechanical and structural integration, the interaction of implant material like zirconia with the host immune system and its biocompatibility plays a pivotal role in determining implant success or failure [21]. The biological interface formed between the implant surface and the surrounding soft and hard tissues is mediated by a cascade of cellular and molecular responses. These responses are not passive but rather reflect a dynamic interaction involving immune cells, cytokines, signaling molecules, and local tissue remodeling events. A balanced immune response can promote wound healing and tissue regeneration, while an excessive or dysregulated immune activation may lead to fibrous encapsulation, peri-implantitis, or even implant failure [22]. Understanding this host immune response to zirconia implants is thus essential in evaluating their biocompatibility and long term clinical performance. Recent findings suggest that zirconia implants elicit a distinct immunological profile compared to their titanium counterparts. Studies have shown reduced bacterial adhesion to zirconia surfaces, potentially lowering the risk of peri-implant disease [23]. In vitro analyses have also demonstrated a lower inflammatory cytokine release and reduced activation of pro-inflammatory immune cells in response to zirconia, supporting its potential as a more immune tolerant material [24-26].

In an era where patient centered care is paramount, the choice of implant material extends beyond mere functional considerations. Furthermore, individual variations in immune responses, systemic health conditions such as diabetes or autoimmune disorders, and lifestyle factors like smoking and oral hygiene all influence the healing trajectory and final outcome of dental implants [27] [28] [29] [30]. Zirconia dental implants represent a promising evolution in implant technology, offering potential advantages in both biological and aesthetic realms. Despite the promising developments, long term clinical trials comparing zirconia and titanium implants are still limited in number and scope, and heterogeneity in study designs poses challenges in deriving definitive conclusions. Furthermore, the wide variety of surface modifications and implant designs complicates direct comparisons across studies. As such, a comprehensive evaluation of the current evidence is necessary to clarify the role of zirconia implants in clinical practice and to identify gaps in knowledge that warrant further investigation. Future research must adopt a more holistic and personalized approach in evaluating zirconia implants, integrating insights from immunology, materials science, bioengineering, and clinical disciplines.

By bridging the gap between fundamental science and clinical application, this review endeavors to provide a roadmap for clinicians, researchers, and implant manufacturers in navigating the opportunities and challenges associated with zirconia implants. In this

review, we summarize the development and material properties of zirconia implants, critically compare osseointegration outcomes with titanium, evaluate host immune responses, and discuss clinical outcomes and future directions.

## Methods

This narrative review was conducted using a structured literature search to ensure transparency and rigor. Databases searched included PubMed, Scopus, and Web of Science, covering publications up to 2025. Keywords used included "zirconia dental implants," "titanium implants," "dental implants," "osseointegration," "immune response," "biocompatibility of dental materials," and related terms. Inclusion criteria encompassed peer-reviewed articles, clinical studies, in vitro and in vivo experiments, systematic reviews, and meta-analyses relevant comparing implant material properties, host tissue responses, and clinical outcomes. Exclusion criteria included non-English publications, case reports with insufficient data, and studies unrelated to dental implantology. While this review is non-systematic, we prioritized high-quality evidence and recent studies to provide a comprehensive and critical overview of zirconia implants and their comparison with titanium.

## Historical Background

The history of dental implants spans over two millennia, with early civilizations in Egypt and South America using materials such as seashells, stones, animal teeth, ivory, bone, and gold to replace missing teeth [31] [32] [33] [34]. Notably, a 600 AD Honduran site revealed shell implants integrated with bone, indicating an early biological response [35] [1]. Medieval attempts using allografts and xenografts often failed due to infection [1]. From the 17th to 18th centuries, various materials and donor teeth were experimented with, but rejection remained a major issue [36]. In the 20th century, modern implant designs emerged: a basket-shaped iridium implant in 1913 [37], threaded cylindrical implants in 1938 [38], [39], and the development of subperiosteal implants, which eventually fell out of favor due to complications [40] [41] [42] [43]. In 1957, a huge advancement in dental implantology occurred, when Brånemark began investigating bone healing and regeneration and found out that not only bone can grow in close contact with titanium (Ti) but also it can form a direct, stable bond with the metal, with no rejection response [44]. Hence, the phenomenon 'osseointegration' was first identified in 1957 by Brånemark who conducted numerous further studies involving both animal models and human subjects. In 1965, Brånemark placed the first four titanium dental implants in a 34-year-old patient's mandible, which, after several months of healing, the titanium fixtures were used as the foundation for a fixed set of prosthetic teeth. Remarkably, these implants functioned successfully for over 40 years, lasting until the patient's death [35] [45]. In 1982, Brånemark presented 15 years of data, establishing titanium as the gold standard for dental implants [46] [47]. Therefore, titanium implants gained FDA approval in 1982, and computer-aided design and manufacturing (CAD/CAM) technology introduced in 1983 enabled precise prosthetic production [1]. Recent research continues to focus on improving materials, technology, and aesthetic outcomes to enhance implant stability and success [48].

Over the past century, several implant techniques have shaped dental implantology. In the early 1960s, endosseous titanium rods were inserted into the jawbone and extended into the oral cavity, but they could not form a stable bone-implant bond [49] [50]. In the mid-1970s, transosteal implants were introduced, involving mandibular exposure and screws to support overdentures, yet their invasiveness and complications limited use [51]. Blade implants, developed in 1987, involved inserting a blade-shaped fixture into a prepared bone slot, but issues such as nerve damage, gingival recession, and bone loss were common [52].

Historically, metals, alloys, ceramics, polymers, glasses, and carbon have been tested for implants [53] [54] [55]. Key requirements for implant materials include biocompatibility (safe interaction with tissues), biofunctionality (mechanical and physical suitability), availability (ease of manufacturing and sterilization), and the ability to achieve osseointegration [56] [57]. Metals are ideal materials for implants, due to their excellent mechanical properties. Stainless steel, gold alloys, cobalt chromium alloys and tantalum are some of the implant materials these days [58]. Pure titanium (cpTi) as one of the most common materials being used in implant industry, various degrees of purity (graded from 1 to 4 in dependence of oxygen, carbon, and iron content). Grade 4 cpTi is the most common used due to its strength. Besides pure titanium, the development of its alloys has provided better durability and strength. Ti–6Al–4V (contains 6 % aluminum and 4 % vanadium) as the most common alloy of titanium being used in dental implants, has better yield strength and fatigue properties than pure titanium [59]. Due to the toxicity of vanadium, new types of alloys like Ti-6Al-7Nb and Ti-5Al-2.5Fe have been developed [60].

Despite the widespread use of titanium and its alloys in modern dental implants, concerns about possible immune responses and esthetic compromises have

prompted researchers to explore alternative materials. Ceramics have emerged as a promising class of implant materials. This group includes diverse options such as alumina oxide, hydroxyapatite (HA), tricalcium phosphate (TCP), silicon nitride, zirconia, and bioglass [58]. Beginning in 1992, advancements in modern ceramic materials have gained momentum, leading dental implant manufacturers to incorporate ceramic surface treatments and ceramic components into their implant systems to enhance osseointegration [61]. Among the materials adopted, high-purity alumina oxide (with a purity greater than 99.5%) became a preferred choice due to its outstanding resistance to corrosion, strong biocompatibility, excellent wear resistance, and mechanical strength [62]. In 1998, Ogiso et al. explored the use of pure dense HA as another ceramic option. Although HA demonstrated favorable chemical stability and biocompatibility, its clinical potential has been limited by insufficient mechanical strength and weak bone formation capabilities [63] [64]. TCP as another ceramic cannot stimulate bone formation or restrain bone resorption, however, exhibits outstanding biocompatibility and osteoconductivity. Zinc has been shown to promote the growth of osteoblasts while simultaneously inhibiting the activity of osteoclasts. This dual effect contributes to improved bone regeneration around implants containing zinc ions, such as those made from TCP [64]. Additionally, silicon nitride has emerged as a ceramic material of interest for implants, exhibiting both effective bone integration and antimicrobial properties in vivo [65]. It also has shown better biocompatibility, stability, and bone respond compared with polyetheretherketone (PEKK) or titanium [66] [67] [68] (Figure 1).

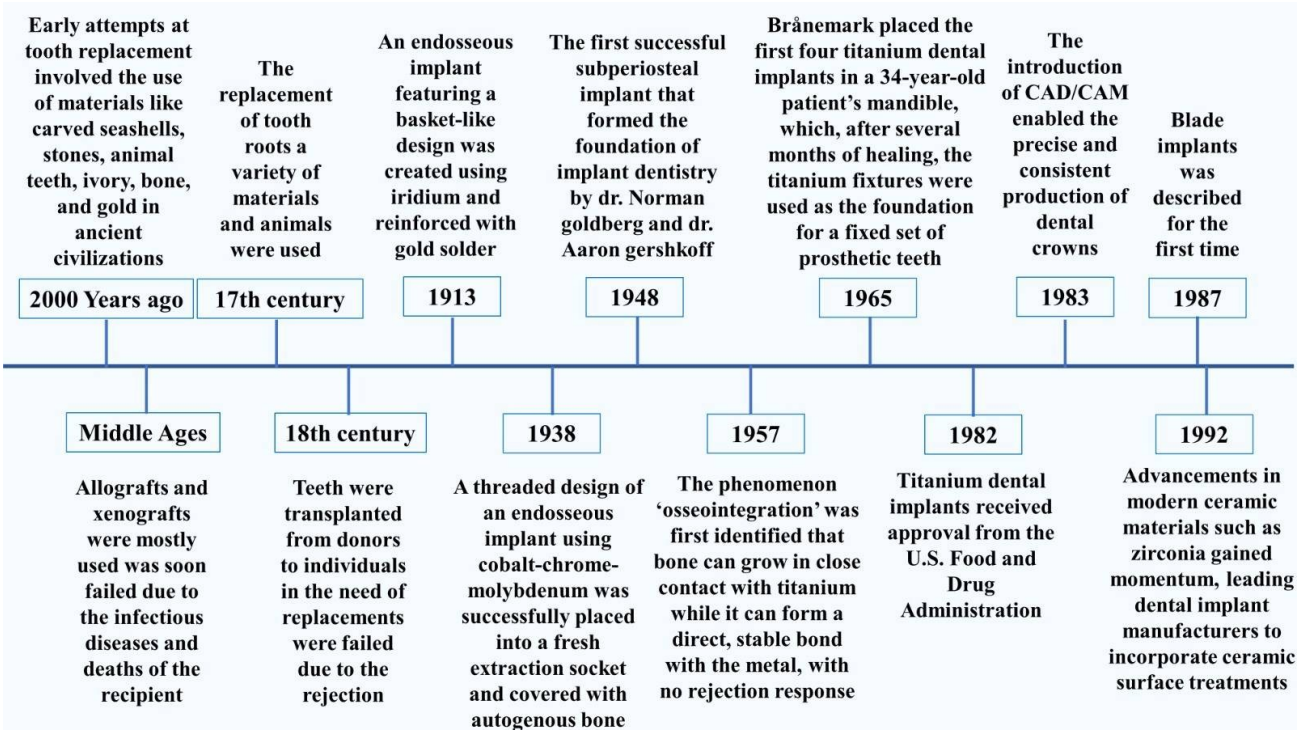


**Figure 1.** Historical timeline of dental implants. The evolution of implantology spans from ancient civilizations to advancements in modern ceramic materials at the end of the 20th century.

In 1969, M. Hodosh and colleagues introduced polymethacrylate tooth-replica implants, marking early use of biologically compatible polymers in dentistry [69]. These implants effectively restored function and aesthetics [70]. Synthetic polymers like PEEK (semi-crystalline thermo-plastic polymer), BisGMA/TEGDMA composite, and PEKK, bio-polymers such as PLA (polylactic acid) and chitosan offer advantages over metals, including tunable properties, ease of fabrication, improved tissue integration, reproducibility, and superior aesthetics [71] [72].

## Zirconia Implants

Zirconia, a metal dioxide first discovered in 1789, possesses mechanical characteristics that are quite similar to those of metals [73]. It exists in three distinct crystallographic phases depending on temperature. At room temperature and up to 1170 °C, it adopts a monoclinic (m) form. When heated between 1170 and 2370 °C, the structure transforms into a tetragonal (t) phase, and it becomes cubic (Fm3m) at temperatures above 2370 °C, persisting until it reaches its melting point [74]. The incorporation of stabilizing oxides such

as CaO, MgO, $Y_2O_3$, or $CeO_2$ into pure zirconia enhances its fracture resistance by preventing crack propagation [75]. Among the various stabilized forms, yttria-stabilized tetragonal zirconia polycrystals (Y-TZP) are especially notable for their superior mechanical strength, wear resistance, and compatibility with biological systems, making them suitable for dental implant fabrication. Medical-grade zirconia typically contains 3 mol% of $Y_2O_3$ as a stabilizing agent [76] [77]. Research has increasingly highlighted zirconia as a favorable biomaterial, primarily because of its outstanding mechanical features [78]. However, concerns remain regarding its durability over extended periods [79]. One such issue is low-temperature degradation (LTD), also referred to as "aging," which can occur even at room temperature in moist environments. The diffusion of water molecules into the zirconia structure induces tensile stress on its surface, lowering the energy threshold required for phase transformation and consequently facilitating the monoclinic transition [80] [81]. Despite these challenges, Shimizu et al. reported that zirconia implants maintained their mechanical integrity even after 30 months in the tibial bone marrow of rabbits [82]. Notably, recent advancements in processing techniques, such as refining crystal size, eliminating contaminants, and adopting more aging-resistant compositions, have significantly mitigated these aging effects to biologically acceptable levels [83]. Newer zirconia materials have been specifically engineered to address the limitations of conventional 3Y-TZP formulations [77].

Hot isostatic pressing (HIP) is widely used to produce high-density, homogeneous zirconia dental implants. Pressed or partially sintered Y–TZP parts are exposed to high pressure and temperature, improving density, eliminating pores, enhancing mechanical strength, and reducing aging [84] [85] [86]. Presintered blocks (~95% density) are HIPed at 1400–1500 °C, sometimes followed by oxidation to restore whiteness, reaching ~6.09 g/cm³ [46]. Fully densified Y–TZP is hard to machine, requiring durable CAD/CAM milling systems, but yields smooth surfaces [87] [88]. Modern CAD/CAM often uses partially sintered blanks, which are easier to mill and require scaling to compensate for shrinkage, whereas HIPed blanks can be milled directly to final dimensions [89] [90].

Powder injection molding (PIM), also known as ceramic injection molding (CIM), is an alternative approach to traditional machining for fabricating zirconia and other ceramic components. This method combines powder metallurgy with injection molding technology to produce complex-shaped ceramic parts at relatively low cost [91]. The process includes multiple stages: mixing ceramic powders with organic binders to create a feedstock, injecting the feedstock into molds, removing the binder (debinding), and finally sintering the shaped parts. Depending on the type of binder used, the feedstock can be tailored for different plastic shaping techniques [92]. In Park et al. investigation, it was reported that PIM as a new technology was used for preparing rough surface zirconia dental implants which exhibited promising results in an in vivo rabbit experiment [93]. As research continues to address early challenges such as brittleness and limited long term data, zirconia is expected to play an increasingly significant role in the future of implant dentistry.

**Osteointegration of Zirconia Implants**

Osseointegration is defined as a direct bone to implant contact under load. It can also be defined as a direct bone-to-implant contact [47]. Successful osseointegration is a complex process influenced by various biological and mechanical factors. There are six factors that are considered to influence the osseointegration of dental implants: implant material, implant design, surface conditions, status of the bone, surgical technique and implant loading conditions [94]. For a successful osseointegration, cells should adhere to the biomaterial surface. During this initial interaction, the cytoskeleton undergoes reorganization, and communication takes place between the cells and the surrounding extracellular matrix at the interface. These events initiate gene expression and guide tissue-specific remodeling processes. Surface characteristics, such as texture and topography, significantly affect cellular behaviors, including proliferation, differentiation, extracellular matrix production, and even changes in cell shape [95].

The integration between bone and implant follows a biological sequence resembling primary bone healing. Immediately after implantation, a thin water film rapidly forms around the implant surface within nanoseconds, enabling the rapid adsorption of proteins and other crucial biomolecules [96]. Over the following seconds to hours, the implant becomes coated with matrix proteins, initially sourced from interstitial fluids and blood plasma, and subsequently from cellular secretions. The specific structure and composition of this protein layer are strongly influenced by the surface characteristics of the implant [97]. This layer acts as a mediator for cellular attachment, migration, and differentiation, supporting interactions between cells and the implant over a period of hours to days [98]. By the end of the first day, key molecular events begin to unfold: water molecules and platelets at the site initiate the release of growth factors [99]; undifferentiated osteoblasts attach to the surface, aided by fibronectin [100]; and pluripotent mesenchymal cells begin migrating along the implant

surface. Their behavior is influenced by local oxygen tension and angiogenic signaling, which are further affected by the implant's spatial positioning [101]. As the process continues, the biological response is modulated by extracellular matrix (ECM) proteins, cytoskeletal elements, surface binding proteins, and surface chemistry, including topography and ion release [102]. ECM proteins convey critical signals that influence cell morphology, polarity, motility, gene regulation, survival, and proliferation [103]. Proteins such as collagen I, fibronectin, osteopontin, osteonectin, osteoadherin, bone sialoprotein, and plasma proteins like α2HS glycoprotein serve as both structural scaffolds for adhesion and biochemical messengers that facilitate cell to cell and cell protein communication [97]. On the second day, local capillary breakdown causes ischemia and necrosis near the implant site. Neutrophils dominate the inflammatory response, gradually being replaced by macrophages, which contribute to clot formation and the clearance of necrotic tissue [104]. By the third day, osteogenic differentiation is promoted through the activation of transcription factors such as runt-related protein 2 (Runx2) and osteopontin in cells adjacent to the implant [105]. On day four, resorption of necrotic bone begins and a primitive bone and implant interface is established [106]. By the fifth day, signs of new bone formation become apparent. Increased alkaline phosphatase activity reflects the initiation of mineralization and matrix remodeling [105]. By the seventh day, a cohesive bone matrix becomes visibly anchored to the implant surface, and bone to implant contact is approximately 35.8% [105] [107]. At day sixteen, the implant surface becomes fully covered with mineralized tissue, osteoid, and a dense collagen rich matrix [106]. By the twenty eighth day, complete integration is characterized by the formation of a structured tissue layer consisting of collagen fibers and osteoblasts aligned parallel to the implant surface. At this stage, bone to implant increases to approximately 46.3% [107]. Bone regeneration proceeds via two distinct mechanisms: contact osteogenesis, which occurs directly at the implant surface and progresses approximately 30% faster due to favorable surface properties; and distant osteogenesis, which begins at the bone margins and extends toward the implant, resulting in woven bone formation [97] [104]. By the end of the twelfth week, a mature lamellar bone architecture is fully established at the implant interface, forming a uniform and stable bond between bone and implant surface that ensures long-term osseointegration [106]. Once activated, osseointegration progresses through a series of well-orchestrated biological stages, beginning with molecular and cellular events such as protein adsorption, cell adhesion, and inflammatory responses, followed by the formation of woven bone, its maturation into lamellar and parallel fibered bone, and finally, structural bone remodeling in response to mechanical loading [108] (Figure 2).

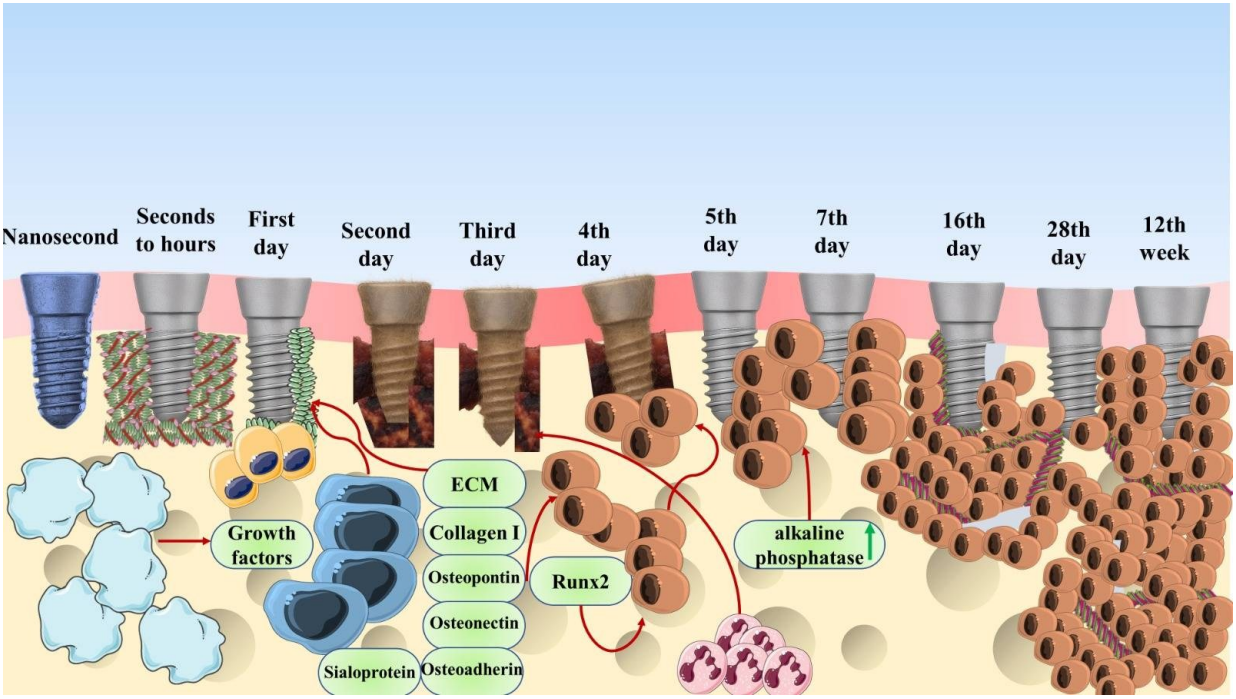


**Figure 2.** The prosses of a successful osteointegration of a zirconia implant. From a thin water film around the implant surface within nanoseconds after implantation to a uniform and stable bond between bone and implant surface that ensures long-term osseointegration.

Ensuring the longevity of endosseous implants relies on effectively regulating the biological and physical complex events that govern osseointegration.

The condition of the surrounding bone plays a vital role in the success of implant integration. Compromised bone quality such as in cases of osteoporosis or prior radiation exposure can significantly hinder the osseointegration process. Therefore, it is generally recommended to postpone implant placement following radiotherapy or to enhance healing outcomes through adjunctive treatments like hyperbaric oxygen therapy. Additional host related risk factors, like a history of smoking, cancer, cancer, xerostomia, and systemic diseases such as diabetes and hypertension, can also negatively affect implant success. In situations where the alveolar ridge has undergone resorption or lacks adequate volume, procedures such as bone grafting or ridge augmentation are necessary to establish a suitable environment for stable osseointegration [109] [57].

Surgical technique is another effective factor that can influence the success of osseointegration. Restricting tissue injury and keeping bone temperature below harmful thresholds during surgical drilling are crucial for preventing unintended bone necrosis. Using low speed drilling techniques helps achieve this. For instance, exposing bone to a temperature of 47°C for just one minute can begin to cause bone necrosis [110].

Achieving successful osseointegration heavily depends on establishing strong primary implant stability at the time of placement. Over time, different implant loading protocols such as immediate, early, and conventional loading have been explored, each yielding variable clinical results. A meta-analysis by Chen et al. found that immediate loading can result in comparable implant survival rates to early loading, though not necessarily to conventional loading [111]. Furthermore, Donati et al. evaluated histological differences between immediately loaded and unloaded implants, reporting no significant difference in bone to implant contact percentage. Interestingly, the peri-implant bone surrounding immediately loaded implants appeared to be denser [112]. These findings suggest that while loading protocols impact initial implant stability and healing dynamics, other factors also play a pivotal role in determining the long-term success of osseointegration.

Implant surface morphology can also affect attachment, proliferation, extracellular matrix synthesis, growth factor release and cytokine production [113]. The properties of a dental implant's surface are crucial in influencing the biological responses that promote successful osseointegration and ensure the implant functions effectively. Specifically engineered microstructured surfaces have been shown to improve the stable integration of transcutaneous implants within connective tissues and may help inhibit undesirable epithelial migration, which can lead to implant failure [114]. The morphology of the implant surface significantly influences how surrounding cells respond, including their attachment, proliferation, and differentiation [115]. These interactions can lead to altered gene and protein expression in bone-forming cells, thereby affecting their phenotype and behavior at the implant interface. Various surface features like topography, surface roughness, oxide layer thickness, elemental composition, and impurity content are largely determined by the specific surface treatment methods applied during manufacturing. However, isolating the effect of a single parameter remains challenging, as modifications often influence multiple surface characteristics simultaneously. For example, changing the chemical structure or crystallinity of the titanium oxide layer typically alters the surface roughness as well [116].

Several surface engineering strategies have been developed to enhance osseointegration. Macrotopographic modifications, such as optimizing thread dimensions, improve primary stability and create healing chambers that support osteogenic cell migration [117]. Microtopography enhancements, typically in the 1–100 μm range, promote osteoblast attachment and bone deposition [118] [119]. Nanotopography, acting at the protein interaction level, further supports cell adhesion and integration through physical, chemical, and biological mechanisms [120] [121]. Enhancing surface wettability by making implants more hydrophilic improves protein adsorption and osteoblast maturation [122]. Photofunctionalization using UV light increases surface bioactivity, reduces hydrocarbons, and improves cellular interaction with aged titanium surfaces [123]. Coating implant surfaces with growth factors, peptides, or therapeutic molecules such as bone morphogenetic proteins or bisphosphonates accelerates healing and addresses local or systemic limitations [124]. Additionally, local drug delivery, such as melatonin administration, has shown potential to improve bone density and osseointegration in early loaded implants [125].

Geometry of implant, width and length of implant, and microdesign of implant are among implant design factors that are important determining the success and failure of osseointegration. Implant geometry plays a vital role in the osseointegration process, as bone tends to form more readily on raised or protruding surface features such as ridges, crests, and thread edges. The overall shape of the implant is also a critical factor, as it influences both the amount of surface area available for stress distribution and the achievement of primary stability. Threaded implants, in particular, provide a

larger functional surface area compared to smooth, cylindrical, or tapered designs. This allows for better mechanical fixation and minimizes movement within the surrounding tissue during the initial healing phase. In contrast, implants with smooth surfaces often require additional surface modifications to enhance integration, and tapered designs, while beneficial in certain clinical situations, may reduce the total area available for bone anchorage. In addition, the greater the dimensions of an implant, the greater is the surface area provided for osseointegration [126].

The material composition of the implant itself is another critical factor influencing the success of osseointegration. As previously noted, the primary materials used for manufacturing dental implants are metal alloys, primarily titanium, iron, and tantalum as well as ceramics like zirconia. Over the past two decades, research interest in stainless steel implants has significantly declined, dropping from 38% to 20%. This shift is largely due to concerns over the presence of toxic impurities in stainless steel and its relatively poor corrosion resistance and biocompatibility. In contrast, titanium and its alloys have consistently maintained a dominant role, accounting for approximately 50% of studies during this period, and currently represent the standard material used in most commercially available dental implants [127].

Zirconia has garnered significant attention as a material for dental applications. The incorporation of Y–TZP enhances its mechanical strength and stability. Due to these advancements, zirconia implants have become a viable option in modern implant dentistry and are increasingly utilized for tooth replacement. One notable advantage of zirconia compared to titanium is its natural ivory-like color, which offers superior aesthetic outcomes. As the impact of surface modifications of zirconia implants on osseointegration is not clear yet, most researches have investigated the effect of modification of zirconia surfaces on osseointegration in experimental animal studies [18]. Most of these studies have demonstrated bone formation on zirconia implants featuring a range of surface modifications, such as sandblasting [128], etching [129], sintering, and coating to increase the surface roughness of machined zirconia implants with the goal of improving osseointegration. [130]. In general, the findings have revealed that zirconia implants with a modified surface integrate into bone in the same way as titanium implants, however, there are limited data on the osseointegration of zirconia implants [131].

**In vivo studies**

Minor modifications to the surface of zirconia implants have been shown to significantly influence bone attachment. A recent investigation using miniature pigs demonstrated that acid etching of sandblasted zirconia implants enhanced bone-to-implant contact compared to sandblasting alone, while alkaline etching reduced this contact. Interestingly, both acid and alkaline treatments increased the presence of multinucleated giant cells on the implant surfaces [132]. Immediate replacement of maxillary central incisors with or without loading, using a novel zirconia implant manufactured via PIM and subjected to blasting and acid etching, showed improved survival rates in both animal models and clinical studies [10]. In another study involving miniature pigs, alumina-toughened zirconia implants were compared with standard zirconia and titanium implants. Commercially pure grade 4 titanium implants underwent alumina sandblasting followed by acid etching with hydrochloric and sulfuric acids, whereas the ceramic implants were treated with alumina blasting and hypophosphorous acid. All implant types achieved successful osseointegration with high bone-to-implant contact at 4 and 8 weeks, although titanium implants demonstrated the greatest bone contact percentages. The occurrence of multinucleated giant cells was observed on all implant surfaces, but titanium implants exhibited less coverage by these cells [133]. Depprich et al. compared bone healing around roughened zirconia and titanium implants of similar shape by placing 48 implants into the tibias of twelve minipigs. Samples collected at 1-, 4-, and 12-weeks post-implantation were examined histologically and ultrastructurally. Both implant materials showed direct bone contact, and while titanium implants had slightly higher bone-to-implant contact based on histomorphometric analysis, the difference was not statistically significant. These results indicate that surface-modified zirconia implants can achieve osseointegration on par with titanium implants [134]. These results support the data reported by Kubasiewicz-Ross et al. showing that zirconia implants with changed surfaces have osseointegration characteristics similar to titanium implants [135]. Similarly, Kohal et al. evaluated loaded zirconia implants against titanium implants and found no significant differences in the degree of osseointegration between the two materials [136]. Dubruille et al. investigated the comparative performance of titanium, alumina, and zirconia implants in a canine model. After a 10-month healing period, bone to implant contact was measured at 68% for alumina, 64.6% for zirconia, and 54% for titanium. Despite these differences, no statistically significant variation was observed among the three implant materials [137]. In a separate study, Stanic et al. evaluated the osseointegration of Y-TZP implants with and without a bioactive glass coating in Sprague-Dawley rats. Scanning electron microscopy (SEM) on histological

sections revealed that both coated and uncoated zirconia implants exhibited excellent biocompatibility; however, the bioactive glass-coated implants demonstrated enhanced bioactivity and greater bone affinity [138]. Further supporting these findings, Scarano et al. examined the early bone response to zirconia implants at four weeks post implantation in rabbits. Their results showed a substantial presence of newly formed bone at the implant surface, with a reported bone to implant contact of 68.4 ± 2.4%. Mature bone with minimal marrow spaces was also observed surrounding the implants. Collectively, these studies confirm that zirconia implants can effectively support osseointegration [139]. In consistent with these findings, one piece zirconia, titanium and PEEK implants achieved successful osseointegration based on clinical and histological findings in a histomorphometric study in dogs [140]. In contrast, Akagawa and colleagues observed significant crestal bone loss surrounding zirconia implants under load, while unloaded implants showed less bone loss; however, the extent of bone to implant contact was comparable between the two groups [141]. However, in a follow up study five years later, the same research group demonstrated that zirconia implants, whether loaded or unloaded, could maintain stable long term osseointegration in beagle dogs [142]. Hoffmann and colleagues investigated the initial bone attachment to zirconia dental implants and compared the results with those from surface-treated titanium implants in rabbits. Light microscopy analysis of the bone-implant interface at 2 and 4 weeks after implantation showed comparable results for both implant types. While titanium implants showed slightly higher bone apposition (68–91%) compared to zirconia (62–80%) at 4 weeks, zirconia implants outperformed titanium at the 2-week mark, indicating favorable early osseointegration [143]. In another study, Lee et al. evaluated nanosurface-modified zirconia implants in rabbits. Despite the surface modification using calcium phosphate, no enhancement in osteoconductivity was observed compared to unmodified zirconia or porous titanium implants. At 3 weeks, porous titanium showed superior bone to implant contact, but the calcium phosphate-modified zirconia implants demonstrated comparable performance to non-modified zirconia, with no statistically significant differences [130]. In agreement with this research, in Rocchietta et al. study, the bone tissue response to zirconia implants with three different surface modifications (Topographically modified zirconia (Zi-Unite), Promimic, CoAT sputtered) was compared to that of oxidized titanium implants, aiming to optimize osseointegration in terms of both strength and speed. The results in this study suggest that additional chemical modifications to topographically treated zirconia surfaces do not necessarily enhance osseointegration or interfacial bonding strength [144]. A study by Plecko et al. demonstrated that in sheep model cobalt-chromium implants coated with titanium or zirconium/titanium alloys combined excellent mechanical strength with favorable osseointegration, making these composite materials promising candidates for orthopedic applications [145].

As mentioned before, PIM is an alternative to classical machining for preparing zirconia and other ceramics. In Park et al. study, the osseointegration of PIM-fabricated zirconia implants in rabbit tibiae produced using molds with and without roughened inner surfaces and included machined titanium implants as a control group was investigated. SEM of the zirconia surfaces formed with roughened molds revealed distinct elevations and depressions, along with the characteristic grain structure typical of as-sintered zirconia. Implants molded with the roughened surfaces showed significantly higher removal torque values compared to those fabricated using smooth molds. Furthermore, these zirconia implants demonstrated notably greater bone to implant contact and removal torque values than the machined titanium implants. Overall, the findings indicated that PIM-produced zirconia implants with surface roughening possess strong osseointegrative potential [93]. The study concluded that (Ti,Zr)$O_2$-coated PIM zirconia implants in rabbits model, both with smooth and rough surfaces, exhibited improved histological outcomes, specifically in terms of bone to implant contact, compared to their uncoated counterparts. However, mechanical anchorage was primarily influenced by surface topography, with rough surfaced implants demonstrating superior retention regardless of coating [146]. Sennerby et al. observed that in rabbits surface-modified (roughened) zirconia implants exhibited significantly improved osseointegration compared to their machined counterparts and demonstrated comparable removal resistance to oxidized titanium implants [147].

**In vitro studies**

In a study by Sun et al., femtosecond laser etching was employed to create microgroove (MG) patterns on zirconia surfaces to explore how modifying surface morphology affects osseointegration. The microgrooved surface demonstrated reduced metal contamination while increasing both surface roughness and hydrophilicity of the zirconia material. The presence of these MG structures was found to alleviate stress on the adjacent bone tissue and enhance osseointegration, as evidenced by improved adhesion, proliferation, and osteogenic differentiation of MC3T3-E1 cells. Additionally, there was an upregulation of osteogenesis-

related genes, including Runx2, alkaline phosphatase (ALP), and osteopontin (OPN). These findings suggest that the microgroove surface pattern on zirconia implants can effectively promote integration with the surrounding bone [148].

### Clinical studies

Clinical studies on zirconia implants are still relatively scarce, and many existing reports face limitations such as brief follow-up periods and small participant numbers. For instance, research by Mellinghoff et al. and Oliva et al [149] [150] showed one-year implant survival rates of 93% and 98%, respectively. In both studies, most failures occurred during the healing phase and were linked to increased implant mobility, while only one implant failed after prosthetic loading due to fracture. Lambrich and Iglhaut compared 127 zirconia implants with 234 titanium implants over an average follow-up of 21.4 months. They found similar success rates for implants placed in the mandible (zirconia 98.4% vs. titanium 97.2%), but zirconia implants performed significantly worse in the maxilla (84.4% compared to 98.4% for titanium), with all failures attributed to mobility during healing [151]. The same findings were observed in Osman et al. investigation. In a randomized controlled clinical trial involving 24 edentulous patients with 129 implants compared zirconia (test) and titanium (control) groups. Each patient received four maxillary implants in a diamond-shaped quad design (one mid-palatal and three anterior crestal) and three mandibular implants in a tripod design (one mid-symphyseal and two bilateral distal). Overall survival was 71.2%, which was low compared with other zirconia implant trials. Mandibular implant survival was 95.8% for titanium and 90.9% for zirconia, while maxillary survival was 71.9% and 55%, respectively, with a significantly higher failure risk in the maxilla. Mean marginal bone loss (MBL) was 0.18 mm for titanium and 0.42 mm for zirconia. In the mandible, MBL was significantly greater around zirconia implants compared with titanium. Additionally, three zirconia implants fractured, two in the maxilla, leading to the recommendation of at least four wide-diameter fixtures for maxillary overdenture support with zirconia implants [152]. In another study, Depprich et al. reviewed clinical studies published between 2006 and 2011 and identified only 17 relevant reports on zirconia implants, with survival rates varying from 74% to 98% over 12 to 56 months [153]. Moreover, Payer et al. documented a 95% survival rate after two years in a group of 19 zirconia implants that were immediately loaded, based on clinical and radiographic evaluations [154]. Oliva et al. conducted a five-year follow-up of 831 one-piece zirconia implants in 371 patients, reporting a survival rate of 95% [155]. Additionally, Kohal et al. observed that one-piece zirconia implants restored immediately had a one-year cumulative survival rate comparable to titanium implants, indicating that zirconia may deliver similar clinical performance under certain loading protocols [156].

Despite promising results reported in some clinical reviews after 60 months of follow up, additional comparative studies are necessary to clearly establish how zirconia implants perform in comparison to titanium implants [157] [158] [16]. Although zirconia dental implants are commercially available and considered a promising ceramic alternative, only a few manufacturers provide supporting research on their products. Currently, the clinical evidence remains limited, preventing their recommendation for routine use in daily practice. Nevertheless, zirconia implants hold potential as a substitute for titanium, though they have yet to be widely adopted in standard clinical treatment.

## Biocompatibility and Host Immune Response of Zirconia Implants

Since the 18th century, dentists have explored the concept of using intraosseous implants; however, these early attempts were frequently unsuccessful due to surgical wound infections and implant rejection. The advent of effective antiseptics marked a turning point, significantly reducing infection risks and contributing to the advancement of dental implantology. In the early stages, clinical efforts primarily focused on developing optimal implant designs both in shape and geometry to minimize rejection and prevent inflammatory responses triggered by masticatory forces on the implant [159]. The oral and maxillofacial region is a complex environment that challenges the biocompatibility and durability of dental materials. Implants are exposed to saliva, food, microbes, and their by-products, as well as fluctuations in temperature, pH, and chemical composition. Acidic conditions, ranging from bacterial biofilms (pH ~2.2) to gastric reflux (pH 0.8–3.5), can affect material stability and performance, requiring careful consideration in clinical applications [160] [161] [162]. Biocompatibility refers to a material's ability to perform its intended function while eliciting an appropriate host response, without causing inflammatory, allergic, immune, or toxic reactions [163] [164] [131]. Current research focuses on understanding tissue responses, such as cell proliferation, immune activity, and cell death, at the material interface, aiming to develop materials with tailored properties that beneficially influence cellular behavior [165]. Implant materials are generally classified as biotolerant, bioinert, or bioactive. Biotolerant materials (e.g., stainless steel, cobalt-chromium alloys, polymers) are tolerated by tissues but lack osteoconductivity, leading to fibrous

encapsulation rather than direct bone contact, and are rarely used today. Bioactive materials (e.g., hydroxyapatite, tricalcium phosphate) interact with bone and may be partially or fully replaced over time, often as surface coatings. Bioinert materials (e.g., titanium, zirconia, corundum ceramics) form stable bonds with bone, promoting osseointegration via contact osteogenesis without degradation. Titanium's rapid oxide layer formation enhances biocompatibility and protects against ion release, while zirconia also supports osteoblast adhesion and proliferation, increasing its clinical use [166] [167] [168] [169] [170] [171] [172].

As mentioned earlier, the immune response is a major factor influencing the biocompatibility of dental implants. Generally, dental implants are identified by the immune system as foreign objects, and their placement can trigger inflammatory responses that may result in implant rejection [173]. The local immune system at the site of implant placement can degrade the implant material by altering the chemical environment such as ion concentrations, pH, and oxidative reactions driven by reactive oxygen species (ROS). It can also damage extracellular matrix structures, potentially compromising or even preventing effective implant fixation within the tissue [174]. Implant placement triggers both immediate and delayed inflammatory responses, involving key immune cells such as monocytes/macrophages and neutrophils. The immediate innate immune response occurs within 4–6 hours and is marked by the opsonization of the implant through blood protein precipitation, platelet aggregation, complement system activation, and, in some cases, the involvement of mast cells, natural killer (NK) cells, T cells, and B cells [175]. The delayed immune response typically arises from the prolonged or excessive activation of the innate immune system, primarily macrophages, and may further involve adaptive immune components, including B and T lymphocytes [176]. This unbalanced and persistent inflammation is characterized by dysregulated production of both pro-inflammatory cytokines (such as Tumor Necrosis Factor-alpha (TNF-α), Interferon-gamma (IFN-γ), Interleukin-2 (IL-2), IL-6, IL-8, and IL-12) and anti-inflammatory, pro-healing, or pro-fibrotic mediators (including IL-4, IL-10, IL-13, Transforming Growth Factor-beta (TGF-β), and Growth Differentiation Factor 15 (GDF15)) [177] [178]. Macrophages play a crucial role in the innate immune system by recognizing the shape, surface features, and material composition of implants. They regulate tissue responses throughout the entire process of implant integration, including the initial acute inflammatory phase, inflammation resolution, tissue repair, fibrous capsule development, and long-term stability [179] [180]. Gaining insight into the cellular and molecular mechanisms that govern biological and immune reactions to foreign materials is vital for the development of advanced implant biomaterials designed to promote controlled integration within targeted tissues or organs [181]. However, implants engineered for improved biointegration often display diminished compressive and tensile strengths, as well as inferior mechanical properties overall, compared to metal implants or natural bone [182]. Consequently, in addition to designing implants with enhanced biocompatibility, therapeutic strategies that modulate biological responses may be necessary to prevent further compromises in the mechanical integrity of ceramic implants [183]. Nevertheless, the development and production of ceramic materials for dental implants is one of the leading trends in the current dental industry.

It was reported that zirconia-based ceramics are chemically inert substances that cause no harmful effects in the body. Due to the refined surface and smoothness of zirconia, it not only helps maintain gingival architecture but also prevents plaque build-up, providing a favorable surface for gingival tissues [131]. In Hisbergues et al. investigation, it was indicated that zirconia was found to permit the synthesis of a diverse array of essential structural proteins by osteoblasts, thereby enabling the elaboration of the extracellular matrix through a process indicative of sustained cellular functionality and biocompatibility. It was also exhibited that zirconia has no pseudo-teratogenic impact and cannot cause irritation in any form [184].

### In vitro studies

Zirconia, in various physical forms, has been tested in vitro on multiple cell types, including fibroblasts, lymphocytes, monocytes, macrophages, and osteoblasts, to assess its cytotoxic potential. In the early 1990s, Bukat and colleagues used SEM to examine adhesion and spreading of 3T3 murine fibroblasts on alumina and sintered zirconia ceramics (Ca-PSZ) disks with 30% porosity [185]. Later in 1993, the effect of material physical form on in vitro biocompatibility was investigated by Ito et al. and Li et al. [186] [187]. Ito et al. compared wear debris of ultra-high-molecular-weight polyethylene (UHMWPE) versus Y-PSZ or titanium alloys in the presence of pseudo-extracellular fluid (PECF) using L929 murine fibroblasts. They observed dose-dependent higher cytotoxicity for zirconia (Y-PSZ) debris compared to titanium alloys [186]. Li and coworkers directly compared Y-PSZ powders and ceramics on human oral fibroblasts using colony-forming efficiency, MTT assays, and ion dissolution tests at 37 °C in saline. They found that zirconia powders were more cytotoxic than ceramic forms [187]. Finally, Dion et al. tested zirconia powders on human umbilical

vein endothelial cells (HUVECs) and 3T3 fibroblasts via indirect contact, assessing proliferation (MTT, total cell protein) and differentiation (immunofluorescence) [188]. Consistent with Harmand et al, they concluded that zirconia powders ($ZrO_2/Y_2O_3$) do not exhibit cytotoxicity in the tested fibroblast cell line [189]. In another study, the cytotoxicity of zirconia on the L929 cell line (mouse fibroblasts) was investigated, revealing that zirconia exhibits zero-grade cytotoxicity [211].

Monocytes, lymphocytes, macrophages, and other circulating immune cells are key targets for in vitro biocompatibility testing. Zirconia powders and particles have been evaluated for cytotoxicity in several studies. Greco et al. found dose-dependent inhibition of human lymphocyte mitogenesis with Ca-PSZ powders, though Ca-PSZ and alumina were less toxic than titanium oxide [190]. Mebouta-Nkamgeu et al. reported higher cytotoxicity of alumina than zirconia on monocyte-to-macrophage differentiation, assessed via X-ray microanalysis, phagocytosis, and respiratory burst [191]. Catelas et al. showed in murine J774 macrophages that cytotoxicity increased with particle size (>2 μm) and concentration, with no significant difference between zirconia and alumina; both, as well as HDPE particles, induced apoptosis [192]. Sterner et al. confirmed that titanium and alumina particles strongly induced TNF-α in human monocytic cells, whereas zirconia had minimal effect [193].

Given that bone is essential for implant integration, biocompatibility tests using osteoblasts are critical. Josset et al.compared human osteoblasts on zirconia and alumina, finding that zirconia showed no cytotoxicity, supported cell proliferation, extracellular matrix synthesis, and did not affect DNA content [170]. Similar results were reported by Torricelli et al. [194] on rat osteoblasts cells (MTT and alkaline phosphatase assays) and reinforced by Lohman et al.[195] and Bächle et al. [196], who observed higher proliferation on zirconia than alumina and no morphological differences across Y-TZP surfaces. Hao et al. showed laser-modified zirconia improved osteoblast adhesion, likely via enhanced wettability [197]. Wang et al. reported that zirconia wear particles, together with macrophage activation, increased $O_2^-$ production by osteoclasts [198], while Liagre et al. found no significant differences in proinflammatory cytokine release or arachidonic acid metabolism between zirconia and alumina particles [199].

### In viv studies

Several animal studies have assessed the behavior of zirconia ceramics in soft tissues. Different physical forms (pins, bars, wear particles) and structural types (TZP, PSZ, coatings) were tested for systemic toxicity and local tissue reactions. In rodents, Y-PSZ implanted in paraspinal muscles or subcutaneously for up to 12 months became encapsulated by a thin fibrous layer (<80 μm), similar to alumina controls, without adverse tissue reactions [200] [201]. Mg-PSZ also showed biocompatibility in rabbit muscle [202]. Flame-sprayed unstabilized zirconia coatings on stainless steel tubes implanted in rabbit and dog tracheas induced minimal fibrous overgrowth but no other adverse effects [203]. Likewise, peritoneal injections of Ca-PSZ or Y-PSZ powders in mice produced no local or systemic toxicity [204] [205]. In Styles et al. study, no cytotoxicity in the soft tissue in relation to wear products of zirconia was reported [210].

The first report of zirconia biocompatibility in hard tissue was by Helmer and Driskell, who implanted 6% $Y_2O_3$-stabilized zirconia pellets into monkey femurs, observing bone ingrowth without adverse reactions [206]. Early comparative studies by Wagner [207] and Christel [208] using Y-TZP or alumina pins in rabbit femurs showed no differences in bone response. Similarly, bars and cylinders of yttria-stabilized zirconia implanted in rat, rabbit, and mouse bones caused no local or systemic toxicity [73]. Similar results were observed in the study by Mai et al. through investigating the histological behavior of zirconia implants [209].

### Immunological responses

Particles generated by shear forces during dental implant placement may provoke inflammatory responses or osteolysis linked to peri-implantitis through the activation of inflammasomes [210]. In Ramenzoni et al. study, the comparison of cytotoxic and pro-inflammatory effects of titanium and zirconia particles in macrophages regarding their nature/particle concentration over time under sterile lipopolysaccharide (LPS) inflammation was investigated. In this study, it was indicated that macrophages exposed to titanium particles exhibited approximately 3.5 times greater gene upregulation compared to those exposed to zirconia, particularly between 12 and 48 hours. Upon co-stimulation with LPS, both titanium and zirconia particles elicited a further increase in pro-inflammatory gene expression like TNF-α, IL-1β and IL-6. These findings indicate that zirconia particles induce lower levels of toxicity and inflammatory cytokine production compared to titanium dioxide [25].

Liagre's study found that zirconia had no significant effect on the production of IL-1 and IL-6 or on arachidonic acid metabolism [199]. Additionally, when comparing neutrophil responses to titanium alloy and zirconia toughened alumina surfaces, no significant differences were observed in neutrophil count, activation status, receptor expression, or cell death [211]. An in

vivo study monitoring inflammatory biomarkers over a 12-month period in seven patients with zirconia implants revealed elevated levels of pro-inflammatory cytokines in the bloodstream, suggesting the presence of chronic systemic inflammation. In fact, elevated levels of pro-inflammatory cytokines observed in the study may stem from various factors, including the underlying clinical oral conditions that led to the patients' enrollment. Notably, high concentrations of the anti-inflammatory cytokine IL-10 were also detected, potentially as a regulatory response to ongoing chronic inflammation. The combination of increased pro-inflammatory cytokine expression and reduced mitochondrial function in cells suggests elevated oxidative stress and a heightened burden on the immune system. These host responses are likely attempts to manage or resolve persistent inflammation. These results highlight the intricate interactions among different cytokines and their importance in maintaining immune balance during chronic inflammation [212]. In a separate study, levels of IL-1RA, IL-8, G-CSF, macrophage inflammatory protein-1β (MIP-1β), and TNF-α were measured around zirconia implants, titanium implants, and natural teeth. After an average follow-up of 2.2 years, it was found that the mean plaque index (PI) was notably lower at zirconia implants compared to natural teeth, whereas the mean gingival index (GI), probing depth (PD), and bleeding on probing (BOP) were significantly greater. The correlation of five biomarkers (IL-1RA, IL-8, G-CSF, MIP-1β, and TNF-α) between zirconia implants and teeth, and of four biomarkers (IL-1RA, IL-8, GM-CSF, and MIP-1β) between zirconia and titanium implants, suggests an individualized inflammatory response pattern in patients. However, the levels of IL-1β and TNF-α were significantly elevated around zirconia implants compared to natural teeth. These results underscore the complexity of peri-implant tissue responses and support the notion that host specific immune mechanisms may influence clinical outcomes across different implant materials [24]. It was also reported that unlike metal implants, zirconia implants are considered hypoallergenic. Meanwhile, titanium hypersensitivity can sometimes develop years after implantation, presenting as itching and irritation around the implant site [213].

The complement system is a vital element of the innate immune response, playing a central role in defending against microbial infections and facilitating the clearance of immune complexes and damaged cells [214]. In Jiang et al. study it was reported that on zirconia surfaces, more adsorption of immunoglobulin G (IgG) and complement protein C1q together with the more efficient triggering of the complement system is occurred. Insights from molecular dynamics simulations suggest that the hydrophobic properties of zirconia surfaces increase the availability of IgG binding sites, thereby promoting more robust complement activation. The observation that hydrophilized zirconia elicits a weaker inflammatory response compared to its untreated counterpart underscores the role of surface hydrophobicity in amplifying zirconia-induced inflammation. These findings indicate that structural alterations and increased adsorption of IgG and C1q on zirconia surfaces enhance complement activation, which in turn stimulates macrophage-driven inflammation [215].

**Bacterial colonization**

The oral cavity, with its constant temperature and humid environment, hosts over 500 microbial species that form dynamic biofilms influencing oral health [216]. Factors such as saliva composition, pH shifts, diet, and immune responses shape this ecosystem. Dental materials, including implants, provide nonshedding surfaces that facilitate biofilm formation, which, when uncontrolled, can lead to pathologies like gingivitis, periodontitis, or peri-implantitis [217]. Surface properties—roughness (>0.2 μm), free energy, and chemical composition—critically affect bacterial adhesion [216].

Around implants, the microflora resembles that of natural teeth, with pathogens like *A. actinomycetemcomitans* and *P. gingivalis* implicated in peri-implant disease [218]. Titanium studies confirm that surface roughness promotes plaque accumulation both in vivo and in vitro [219]. Coatings such as TiN or ZrN reduce bacterial colonization, with ZrN being particularly effective [220] [221]. Other surface modifications, including chemical grafting, are under investigation for minimizing bacterial adhesion [222]. Comparative studies of zirconia remain limited. Rimondini et al. reported reduced early bacterial adhesion on zirconia (Y-TZP) versus titanium, both in vitro and in vivo, suggesting immature plaque formation [223]. Scarano et al. confirmed significantly lower bacterial colonization on zirconia, possibly due to its surface conductivity [224]. Scotti et al. found no difference between polished and glazed zirconia regarding bacterial presence, though glazed surfaces showed slightly higher accumulation [225].

In conclusion, given the limited studies on bacterial adhesion to zirconia, current evidence suggests zirconia may reduce bacterial load on its surface. Zirconia implants offer a favorable immune profile and high biocompatibility, making them an increasingly preferred option, particularly for patients with metal sensitivities or aesthetic demands. However, some concerns remain regarding the induction of immune responses and inflammation. Continued research should focus on

developing new strategies in surface engineering, understanding host–material interactions, and achieving controlled modulation of inflammation at the implant site to further improve the clinical performance of zirconia-based biomaterials. Table 1 provides a concise summary of the current evidence on the biocompatibility and host immune response of zirconia implants, highlighting their interactions with both hard and soft tissues as well as immune modulation compared to titanium.

## Future Directions of Zirconia Implants

As the global demand for aesthetically pleasing, biocompatible, and durable dental prosthetics continues to grow, zirconia dental implants have emerged as a promising alternative to conventional titanium-based systems. While zirconia offers several advantages, such as enhanced esthetics, favorable tissue response, and resistance to corrosion, its clinical adoption is still limited due to various unresolved challenges [226]. Consequently, the future of zirconia dental implants depends heavily on overcoming current limitations, improving material properties, refining implant design, and establishing long-term clinical evidence.

### Improving mechanical properties and fracture resistance

One of the most significant limitations of zirconia implants is their inherent brittleness and susceptibility to catastrophic failure under certain loading conditions [227] [228]. Unlike metals, ceramics like zirconia do not exhibit plastic deformation, making them vulnerable to fracture initiation and propagation [229]. Kohal et al. reported a decrease in fracture strength resistance following the cyclic loading and implant preparations [230]. Therefore, enhancing the mechanical strength and toughness of zirconia remains a critical area of future exploration [227]. Emerging approaches include the development of Y-TZP formulations with optimized grain sizes [231] [232], the incorporation of alumina or ceria to create composite ceramics [233] [234] [235], and the use of HIP during fabrication to eliminate internal defects [236] [237] are some new strategies that are under investigation. Additionally, functionally graded materials (FGMs), where the composition or structure varies throughout the implant, may offer a solution by combining the strength of core materials with a bioactive surface layer [238] [239] [240]. Researchers are also investigating surface engineering techniques such as laser shock peening [241] [242] [243] and femtosecond laser treatments to improve fatigue resistance and mechanical behavior under cyclic loads [244] [245] [246]. Continued advances in materials science and nanotechnology are expected to further increase the reliability and durability of zirconia implants [247].

### Enhanced Osseointegration and Bioactivity

Although zirconia demonstrates satisfactory osseointegration, future developments should focus on modifying the zirconia surface to enhance cellular responses and accelerate bone to implant contact. Various strategies have been developed, including surface topography modifications through sandblasting [248], acid etching [155], or laser structuring [249] to promote osteoblast attachment and differentiation, surface functionalization of zirconia implant using coatings with hydroxyapatite (HA) [250] [251], calcium phosphate [252] [253], or bioactive peptides [254] to improve osteointegration and biological interactions, nanostructured surfaces that mimic the extracellular matrix to provide optimal cues for stem cell behavior and new bone formation [255], drug-eluting zirconia implants, capable of releasing anti-inflammatory [256] or osteoinductive agents to prevent infections and enhance osseointegration [257] [258] [259].

### Design Optimization and Digital Integration

Traditional implant shapes and macrodesigns were largely developed for titanium systems and then adapted for zirconia. However, the distinct material characteristics of zirconia warrant a re-evaluation of implant geometry, thread patterns, and connection types to optimize mechanical performance and stability. Finite element analysis (FEA) and 3D simulation have been employed to design implant shapes that minimize stress concentrations and improve load distribution [260] [261] [262]. Sala et al. conducted a study comparing the five-year survival rates, as well as biological and mechanical complications, of one-piece versus two-piece zirconia implants. Their findings showed no significant relationship between implant survival and the occurrence of mucositis in either implant design [263]. These results support the findings in Barros Pascoal et al. study [264]. However, it is important to note that one-piece zirconia implants eliminate the micro-gap and can be restored as natural teeth, but they pose challenges in prosthetic angulation and surgical placement, while there are some issues related to abutment connection strength with teflon, titanium, gold or ceramic screws and cementation about two-piece systems [265]

**Table 1.** Biocompatibility and host immune response of zirconia implants

| Aspect | Findings/Characteristics | References |
|---|---|---|
| General Biocompatibility | Chemically inert, non-toxic, no pseudo-teratogenic effects, no irritation; supports extracellular matrix protein synthesis by osteoblasts. | [131], [184] |
| Soft Tissue Response | Promotes gingival attachment; smooth surface reduces plaque accumulation and maintains peri-implant tissue health. | [131], [299] |
| Hard Tissue Response | Enhances osteoblast adhesion and proliferation; histological studies confirm good bone integration (osseointegration). | [170], [171], [206], [300], [209] |
| Cytotoxicity | No significant cytotoxicity reported in vitro on fibroblasts, lymphocytes, monocytes, and macrophages; zero-grade cytotoxicity in L929 cells. | [184], [301] |
| Inflammatory Response vs. Titanium | Zirconia particles elicit lower inflammatory cytokine production (TNF-α, IL-1β, IL-6) compared to titanium; reduced macrophage activation. | [25], [184] |
| Cytokine Modulation | Some studies show elevated IL-1β and TNF-α levels around zirconia implants; IL-10 also elevated, suggesting compensatory anti-inflammatory regulation. | [24], [212] |
| Immune Hypersensitivity | Zirconia considered hypoallergenic; titanium hypersensitivity (itching, irritation) may appear years after implantation. | [213] |
| Complement System Interaction | Zirconia surfaces adsorb more IgG and C1q, enhancing complement activation; hydrophilic surface treatment reduces inflammatory response. | [215] |
| Long-term In Vivo Findings | Stable fibrous capsule formation (<80 μm) in soft tissue; no significant degradation after 12 months implantation. | [200], [201] |
| Bacterial Colonization | Zirconia appears to lower bacterial colonization on its surface | [223], [224], [225] |

The findings in Bollen study, suggest zirconia implants a valuable alternative and solution for patients requesting a complete metal-free restoration [265]. Integration of CAD/CAM technologies and 3D printing for customized implant designs and abutments tailored to the patient's anatomical and esthetic requirements are among other modern strategies that are under investigation [266] [267] [268]. Machine learning and artificial intelligence (AI) can also be used to predict implant success rates and to aid in surgical planning based on patient-specific data [269] [270]. As digital dentistry continues to advance, the synergy between zirconia implants and computer-aided technologies will offer more efficient, accurate, and personalized solutions for both clinicians and patients.

**Long-Term Clinical Evidence and Standardization**

Despite the growing number of in vitro and animal studies, the clinical evidence base for zirconia implants is still relatively limited, especially for long term outcomes beyond 5 or 10 years. Well-designed randomized controlled trials and multicenter cohort studies are needed to provide robust data on survival rates, marginal bone loss, biological complications, and patient satisfaction. Comparison studies between zirconia and titanium implants in different patient populations and oral environments [271] [272] [273], evaluation of peri-implant soft tissue health, particularly concerning mucosal thickness, keratinization, and inflammatory markers [274] [275], monitoring of esthetic outcomes, including the color stability of zirconia implants over time in the presence of soft tissue and prosthetic materials [276], assessment of implant success in medically compromised patients, such as those with diabetes [277], osteoporosis [278], or immunosuppression [279] [280] are among key areas for clinical investigations. Furthermore, the lack of standardized testing protocols, surface characterization methods, and classification systems for zirconia implants creates difficulty in comparing studies and interpreting data.

**Antibacterial Surfaces**

Peri-implantitis remains one of the leading causes of implant failure [281]. Zirconia implants have been reported to resist bacterial adhesion and biofilm formation better than titanium, attributed to their surface properties such as hydrophobicity and electrical conductivity [282]. Roehling et al. compared biofilm

formation on pure titanium and zirconia surfaces using a three-species model (*P. gingivalis, F. nucleatum, S. sanguinis*) and human plaque, showing significantly thinner biofilms on zirconia after 72 h, although biofilm metabolism remained similar [283]. An in vivo study further found that titanium implants harbored more bacteria, including *T. forsythia* and *P. intermedia*, and induced stronger inflammation than zirconia [284]. However, other investigations, such as Siddiqui et al., reported no significant differences in early bacterial colonization between the two materials. These discrepancies likely reflect differences in experimental design, bacterial strains, and surface treatments, underscoring the need for further research on the antibacterial performance of zirconia implants [285]. Although zirconia has demonstrated lower bacterial adhesion compared to titanium [224] [286], it is not immune to biofilm formation, however, less accumulation on zirconia implants was reported compared to titanium implants [287]. The development of antibacterial zirconia surfaces is an important frontier. Photocatalytic coatings using titanium dioxide [288] [289], incorporation of silver [290], copper [291], or zinc [292] nanoparticles for their broad-spectrum antimicrobial properties, surface grafting of antimicrobial peptides, enzymes, or polymers that prevent initial bacterial colonization [293] [294], and use of plasma treatments or UV irradiation to modify surface energy and create bacteriostatic environments [295] [296] should be among innovations aim to maintain a healthy peri-implant microbiome and reduce the risk of inflammation, while ensuring that host cell attachment and differentiation are not compromised. Table 2 summarizes the principal directions for future research and development of zirconia implants, encompassing strategies to improve mechanical properties and fracture resistance, approaches to enhance osseointegration and bioactivity, optimization of implant design with integration of digital technologies, the generation of robust long-term clinical evidence and standardization, and innovations in antibacterial surface modifications.

For the replacement of a single tooth, using a single dental implant can offer a more cost-effective solution compared to a conventional three-unit fixed dental prosthesis. In cases involving multiple missing teeth, implant-supported restorations, whether fixed or removable, tend to involve higher upfront costs. However, they are generally associated with greater improvements in oral health related quality of life when compared to alternative treatment options [297]. Zirconia implant systems are generally more expensive than titanium counterparts, primarily due to complex manufacturing processes and limited availability [298]. Future advancements should aim to streamline production, reduce material waste, and develop more sustainable fabrication methods. The innovations in this area will not only reduce the financial barrier to wider

**Table 2.** Key directions for future research and development of zirconia implants

| Development of zirconia implants | Strategies | | References |
|---|---|---|---|
| Improving mechanical properties and fracture resistance | Development of Y-TZP formulations with optimized grain sizes | | [231], [232] |
| | Incorporation of alumina or ceria to create composite ceramics | | [233], [234], [235] |
| | Use of hot isostatic pressing (HIP) during fabrication to eliminate internal defects | | [236], [237] |
| | Functionally graded materials (FGMs) offer a solution by combining the strength of core materials with a bioactive surface layer | | [238], [239], [240] |
| | Surface engineering techniques such as laser shock peening | | [241], [242], [243] |
| | Surface engineering techniques such as laser femtosecond laser treatments | | [244], [245], [246] |
| Enhancing osseointegration and bioactivity | Surface topography modifications | Sandblasting | [248] |
| | | Acid etching | [155] |
| | | Laser structuring | [249] |
| | Functionalization | Coating with hydroxyapatite (HA) | [250], [251] |
| | | Coating with calcium phosphate | [252], [253] |
| | | Coating with bioactive peptides | [254] |
| | Nanostructured surfaces to increase osteointegration | - | [255] |
| | Drug-eluting zirconia implants | Releasing anti-inflammatory agents | [256] |
| | | Releasing osteoinductive agents | [257], [258], [259] |

| | | | |
|---|---|---|---|
| Optimizing implant design and digital integration | Finite element analysis (FEA) and 3D simulation to design implant shapes that minimize stress concentrations and improve load distribution | | [260], [261], [262] |
| | Integration of CAD/CAM technologies and 3D printing for customized implant designs and abutments tailored to the patient's anatomical and esthetic requirements. | | [266], [267], [268] |
| | Machine learning and artificial intelligence (AI) to predict implant success rates and to aid in surgical planning based on patient-specific data | | [269], [270] |
| Long term clinical evidence and standardization | Comparison studies between zirconia and titanium implants | | [271], [272], [273] |
| | Evaluation of peri-implant soft tissue health | | [274], [275] |
| | Monitoring of esthetic outcomes | | [276] |
| | Assessment of implant success in medically compromised patient | Diabetes | [277] |
| | | Osteoporosis | [278] |
| | | Immunosuppression | [279], [280] |
| Antibacterial surfaces | Photocatalytic coatings using titanium dioxide | | [288], [289] |
| | Incorporation nanoparticles for their broad-spectrum antimicrobial properties. | Silver | [290] |
| | | Copper | [291] |
| | | Zinc | [292] |
| | Surface grafting of antimicrobial peptides, enzymes, or polymers that prevent initial bacterial colonization | | [293], [294] |
| | Use of plasma treatments or UV irradiation to modify surface energy and create bacteriostatic environments | | [295], [296] |

clinical adoption but also align with growing environmental concerns in the dental industry.

The future of zirconia dental implants lies at the intersection of material innovation, clinical validation, and digital integration. With ongoing improvements in mechanical strength, surface bioactivity, and implant design, zirconia is poised to become a mainstay in modern implantology, especially in cases where esthetics, allergy concerns, and biocompatibility are paramount. However, to fully realize this potential, it is imperative that researchers, manufacturers, and clinicians collaborate to generate long term clinical evidence, establish standards, and develop accessible, high-performance zirconia implant systems. As these goals are progressively met, zirconia implants may not only complement but potentially rival titanium implants in both functional and esthetic applications.

## Conclusion

This review has highlighted the current evidence on zirconia implants, focusing on their osseointegration, biocompatibility, and host immune response. Zirconia demonstrates favorable osteointegration, biological and mechanical properties, as well as reduced bacterial adhesion and a hypoallergenic profile, which make it an attractive alternative to titanium. However, clinical data remain limited, especially regarding long-term survival and performance in challenging anatomical sites such as the maxilla. While recent advances in surface modification, antibacterial coatings, and digital workflows hold promise, zirconia cannot yet be considered a proven substitute for titanium. Continued high-quality clinical trials and systematic evaluations are needed to define its role in implant dentistry.

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**Availability of data and materials**
The data that support the findings of this study are available from the corresponding author, upon reasonable request.

**Conflict of interests**
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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